responsible were anti-c (or anti-c + E). Fraser and Tovey[2] reported similar findings from south-west England with 1099 cases of haemolytic disease investigated between 1966 and 1968; of these, 70 (60%) were due to anti-c. By 1974 prophylactic treatment had cut the total number of affected babies born in the region to 106 and the proportion caused by anti-c had risen to 12%. In about one-third of cases due to anti-c Fraser and Tovey found that the mother had received a blood transfusion before pregnancy.

As a result of these and other surveys Hardy and Napier[3] have published a comprehensive analysis of 733 Rh-positive women with red cell antibodies found during antenatal testing in South and mid-Wales of more than 380 000 expectant mothers over the 30 years 1948-78. In 81% of the immunised Rh-positive mothers the antibodies could be classed as anti-rhesus, predominantly anti-E, anti-c, or anti-c + E. Of 136 with antibodies outside the rhesus system, most were anti-Kell (71%) or anti-Fy^a (13%). Transfusion history differed in those mothers who had developed anti-rhesus antibodies and those with antibodies outside the rhesus system: 71% of those with non-rhesus antibodies gave a history of previous blood transfusion, compared with 21% when the antibodies were anti-rhesus.

The incidence of haemolytic disease in the babies born to mothers also differed in these two groups. When the maternal antibody was anti-rhesus half the babies were affected compared with only a quarter when the antibodies were non-rhesus. Perinatal mortality was the same in both groups (2·5-3·0%), though when the fetomaternal incompatibility was due to a rhesus antigen 15% of affected babies required transfusion, compared with 6% when the antibody was non-rhesus. In a similar report from Australia[4] Beal found that babies born to Rh-positive women and affected with haemolytic disease rarely required transfusion unless the antibodies responsible were anti-rhesus or anti-Kell. Hardy and Napier's survey[3] confirms the generally held view that babies born to Rh-negative mothers with anti-D are more severely affected, perinatal deaths being more than three times as great (11%) and the need for treatment by transfusion 40-45%.

Hardy and Napier's findings[3] underline the importance of rhesus anti-c as a cause of haemolytic disease of the newborn as seen today. Almost 90% of c-positive infants born to women with anti-c in South and mid-Wales had evidence of haemolytic disease as judged by a positive direct antiglobulin test, and 20% needed transfusion. Neither the overall frequency of the disease nor its severity in affected babies is sufficient, however, to warrant attempted prophylaxis by the injection of c-negative mothers with anti-c immunoglobulin. Clarke and Whitfield[5] found that a total of 85 babies died from haemolytic disease of the newborn in England and Wales in 1978 but that only three had been born to Rh-positive women. Fraser and Tovey[2] recommend c typing of all premenopausal women being given blood transfusions and the issue of c-negative and Kell-negative blood for emergency transfusion to patients known to be Rh-positive. Since nearly all c-negative donor bloods lack the E antigen these are practicable steps which would minimise the formation of anti-c, anti-E, and anti-Kell antibodies—the predominant causes of haemolytic disease when an Rh-positive mother gives a history of blood transfusion. When the affected baby requires treatment by exchange or intrauterine transfusion, the blood for transfusion must not react with the mother's antibodies—that is, c-negative blood is required when the causative antibody is anti-c or Kell-negative if anti-Kell.

Routine antenatal examination for irregular blood group antibodies is of importance not only to identify the few Rh-positive mothers who are carrying a baby affected with haemolytic disease but also to ensure that compatible blood will be available should the mother herself require a blood transfusion. Clearly such antibodies are best detected and identified at a time other than in a clinical emergency. Blood samples from all expectant mothers should be screened for antibodies early in the pregnancy. When a woman is Rh-positive and no irregular antibodies are detected further testing later in the pregnancy will be indicated when there is a history of blood transfusion. In all such cases repeat tests for irregular blood group antibodies should be made on samples collected at the 28th and 34th weeks of pregnancy.

1 Giblett ER. Blood group antibodies causing hemolytic disease of the newborn. *Clin Obstet Gynecol* 1964;**7**:1044-55.
2 Fraser ID, Tovey GH. Observations on Rh iso-immunisation: past, present and future. *Clin Haematol* 1976;**5**:149-63.
3 Hardy J, Napier JAF. Red cell antibodies detected in antenatal tests on rhesus positive women in South and mid-Wales, 1948-78. *Br J Obstet Gynaecol* 1981;**88**:91-100.
4 Beal RW. Non-rhesus (D) blood group isoimmunization in obstetrics. *Clin Obstet Gynecol* 1979;**6**:493-508.
5 Clarke C, Whitfield AGW. Deaths from rhesus haemolytic disease in England and Wales in 1978: accuracy of records and assessment of anti-D prophylaxis. *Br Med J* 1980;**281**:781-2.

Teratogenic risks of antiepileptic drugs

The incidence of congenital malformations in the children of mothers with epilepsy is estimated to be two to three times the usual rate.[1 2] The common major anomalies include cleft lip and palate and congenital heart lesions; malformations of the skeleton, central nervous system, and gastrointestinal tract also occur. The offspring of epileptic mothers have also been reported to have a lower birth weight and a higher perinatal mortality rate.[3] The increased frequency of malformations in children born to epileptic mothers has been attributed to the teratogenic effects of antiepileptic drugs, an association supported by animal experiments.[4] Phenytoin in particular but also phenobarbitone and primidone have been incriminated; sodium valproate is also teratogenic in animals but apparently carries little risk in man, though it cannot be exonerated completely as it has not been used as long as the others. A report from Finland[4a] shows that the mean head circumference of infants of epileptic mothers exposed to carbamazepine and drug combinations that included phenobarbitone and primidone were smaller than in controls. Most of the individual values, however, were still normal; and it has not been established that a subtle reduction in head size reflects a drug effect on the fetal brain. Reports of a "fetal trimethadione syndrome" suggests that the diones carry a high risk and should be avoided in pregnancy[5 6]; in any case they have been superseded in Britain for the treatment of petit mal by ethosuximide and sodium valproate.

One controversial aspect of this problem is the so-called "fetal hydantoin syndrome." The features described are craniofacial and distal limb dysmorphosis,[7-11] including a broad low nasal bridge, epicanthic folds, short upturned nose, hypertelorism, ocular abnormalities, prominent and slightly malformed or low set ears, wide mouth with prominent lips, and variations in the size and shape of the head; while hypoplasia of the distal phalanges and nails with irregular ossification produces short, narrow, and misshapen ends to fingers and

sometimes toes, finger-like thumbs, variations in the palmar creases, and low-arch dermal ridge patterns. Other common features include retarded growth before and after birth, relative microcephaly, and mild-to-moderate degrees of mental handicap. There have also been some recent reports of an association of neuroblastoma with the fetal hydantoin syndrome, suggesting that phenytoin alone, or in combination with other antiepileptic drugs, may rarely cause transplacental carcinogenesis as well as teratogenesis.[11a]

Hanson *et al*[12] reported that about 11% of infants exposed to hydantoins in utero had a pattern of abnormalities consistent with the fetal hydantoin syndrome while an additional 31% showed several of the abnormalities to a minor degree. Some of the abnormalities are not readily apparent in the neonatal period and thus may be overlooked. Furthermore, none of the changes are specific to infants exposed to hydantoin and dispute continues about whether the syndrome is a true entity. Critics of the studies refer to the possible observer bias and lack of precise definition of some of the abnormalities.[13-15] When the malformation rate in children born to a group of epileptic mothers who received hydantoins during their pregnancy is compared with the rates in a group who did not and in a third group of non-epileptic mothers, many other variables have to be taken into account[16-18]—including, for example, the higher incidence of congenital malformations in the families of epileptics.

Epilepsy is not a homogeneous entity and teratogenicity has multifactorial mechanisms. Antiepileptic drugs such as phenytoin, either alone or in combination with phenobarbitone or primidone, affect both maternal and fetal metabolism. Other factors directly or indirectly associated with the epileptic disorder of the pregnant woman that also need to be considered include the aetiology, type, and severity of her epilepsy; the effect of seizures on the fetus; the mother's genetic, obstetric, socioeconomic, and environmental background; and the genetic susceptibility of the fetus.

Certainly the incidence of malformations in babies born to epileptic mothers who have taken antiepileptic drugs during pregnancy is higher than in babies born to epileptic mothers not on treatment,[1] but even those findings need to be interpreted with caution. Firstly, epileptic mothers not taking antiepileptic drugs constitute a small proportion of epileptic mothers: they probably have less severe forms of epilepsy, and various other reasons might account for their not taking drugs during pregnancy. Next, the husbands of mothers with epilepsy on treatment may have a greater tendency to contribute risk factors. Friis[19] showed that both the mothers and the fathers of children with cleft lip and palate had an incidence of epilepsy two to three times higher than expected, and that not all epileptic parents were on treatment with antiepileptic drugs. Possibly factors associated with epilepsy in either parent may be concerned in the higher incidence of congenital malformations in their offspring. The possibility of interaction of parental factors with drugs implies that antiepileptic drugs may have teratogenic effects in certain settings.

While no relation has yet been established between concentrations of antiepileptic drugs in the blood of epileptic mothers and the incidence of malformed children, doctors should take care to avoid both excessive doses and blood concentrations during pregnancy, especially in the early stages. Further carefully planned prospective studies are required to examine the role of hydantoins and other antiepileptic drugs in producing congenital malformations and the mechanism by which they might do so: we need to separate the contribution made by drugs from the part played by the epileptic disorder, and to determine what other factors besides genetic ones determine the susceptibility of some pregnant women with epilepsy to produce malformed babies—and whether this depends on pharmacological differences in drug metabolism, combinations of drugs, or other interactions.

As in our recent leading article on the management of epilepsy in pregnancy,[20] our conclusion is that on balance, although phenytoin and other antiepileptic drugs appear to carry a teratogenic risk, it does not justify (with the exception of the diones) discouraging a woman who needs anticonvulsant treatment from having a child or changing a satisfactory drug regimen when the epilepsy is well controlled. Doctors should explain to parents[21] that the increased risk is small and that many of the complications are minor or remediable; and if carcinogenesis is queried, they can be reassured that this is an extreme rarity. The vogue for single-drug treatment of epilepsy[22] is commendable. Until further facts about the teratogenic risks of antiepileptic drugs are known, their various other side effects also need to be considered, and on balance carbamazepine or sodium valproate seems preferable to phenytoin or phenobarbitone as the first choice for the treatment of appropriate types of epilepsy in young girls and women in their reproductive years.

1 Janz D. On major malformations and minor abnormalities in the offspring of parents with epilepsy, In: Bossi L, Dam M, Helge H, Janz D, Richens A, Schmidt D, eds. *Epilepsy, pregnancy and the child*. New York: Raven Press (in press).

2 Nakane Y. Congenital malformation among infants of epileptic mothers treated during pregnancy—the report of a collaborative study group in Japan. *Folia Psychiatr Neurol Jpn* 1979;**33**:363-9.

3 Bjerkedal T, Bahna L. The course and outcome of pregnancy in women with epilepsy. *Acta Obstet Gynecol Scand* 1973;**52**:245-8.

4 Eadie MJ. Unwanted effects of anticonvulsant drugs in the treatment of epilepsy. In: Tyrer JH, ed. *Current state of modern therapy, vol 5*. Lancaster: MTP Press, 1980;129-60.

4a Hiilesmaa VK, Teramo K, Granström M-L, Bardy AH. Fetal head growth retardation associated with maternal antiepileptic drugs. *Lancet* 1981;ii:165-7.

5 Zackai EH, Mellman WJ, Neiderer B, Hanson JW. The fetal trimethadione syndrome. *J Pediatr* 1975;**87**:280-4.

6 Feldman GL, Weaver DD, Lovrien EW. The fetal trimethadione syndrome. Report of an additional family and further delineation of this syndrome. *Am J Dis Child* 1977;**131**:1389-92.

7 Loughnan PM, Gold H, Vance JC. Phenytoin teratogenicity in man. *Lancet* 1973;i:70-2.

8 Hill RM, Verniaud WM, Horning MG, McCulley LB, Morgan NF. Infants exposed in utero to antiepileptic drugs. *Am J Dis Child* 1974;**127**:645-53.

9 Barr M, Poznanski AK, Schmickel RD. Digital hypoplasia and anticonvulsants during gestation: a teratogenic syndrome? *J Pediatr* 1974;**84**:254-6.

10 Hanson JW, Smith DW. The fetal hydantoin syndrome. *J Pediatr* 1975;**87**:285-90.

11 Hanson JW, Smith DW. Are hydantoins (phenytoins) human teratogens? *J Pediatr* 1977;**90**:674-5.

11a Ehrenbad LT, Chaganti RSK. Cancer in the fetal hydantoin syndrome. *Lancet* 1981;ii:97.

12 Hanson JW, Myrianthopoulos NC, Harvey MAS, Smith DW. Risks of the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome. *J Pediatr* 1976;**89**:662-8.

13 Shapiro S, Slone D, Hartz SC, *et al*. Are hydantoins (phenytoins) human teratogens? *J Pediatr* 1977;**90**:673-4.

14 Apt L, Gaffney WL. Is there a "fetal hydantoin syndrome?" *Am J Ophthalmol* 1977;**84**:439-40.

15 Stumpf DA, Frost M. Seizures, anticonvulsants, and pregnancy. *Am J Dis Child* 1978;**132**:746-7.

16 Monson RR, Rosenberg L, Hartz SC, Shapiro S, Heinonen OP, Slone D. Diphenylhydantoin and selected congenital malformations. *N Engl J Med* 1973;**289**:1049-52.

17 Livingston S, Berman W, Pauli LL. Maternal epilepsy and abnormalities of the fetus and newborn. *Lancet* 1973;ii:1265.

18 Shapiro S, Slone D, Hartz SC, *et al*. Anticonvulsants and parental epilepsy in the development of birth defects. *Lancet* 1976;i:272-5.

19 Friis ML. Epilepsy among parents of children with facial clefts. *Epilepsia* 1979;**20**:69-76.

20 Anonymous. Epilepsy and pregnancy. *Br Med J* 1980;**281**:1087-8.

21 Baraitser M. Epilepsy. *Hospital Update* 1981;**7**:139-47.

22 Feely MP, Callaghan MN. Changing to single drug therapy in epilepsy. *Lancet* 1981;i:847.